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# The microbiota as a component of the celiac disease and non-celiac gluten sensitivity

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SUMMARY

Dietary gluten present in wheat, rye and barley induces several gastrointestinal disorders, including celiac disease and non-celiac gluten sensitivity (NCGS). Celiac disease is an immune-based enteropathy triggered by ingestion of gluten in genetically susceptible individuals resulting from the interaction between genetic and environmental factors. Although gluten has been recognized as the main environmental trigger of the disease, a specific role for the intestinal microbiota in celiac disease development has been suggested. NCGS individuals develop adverse reactions after the exposure to gluten. Due to the similarities in clinical outcomes and the absence of diagnostic biomarkers, it is challenging to differentiate NCGS from celiac disease. The aetiology of NCGS remains unknown, although the involvement of innate immune mechanisms has been suggested. Since the influence of intestinal microbiota on immune cell homeostasis and on education of both innate and adaptive immune system is well known, the role of host-microbe interactions in the non-celiac gluten sensitivity have been hypothesized.

This review aims to summarize the current knowledge of the contribution of microbiota to the pathogenesis and/or onset of celiac disease. In addition, a brief overview of the possible role of the microbiota components on the NCGS is presented.



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## 1. Introduction

Gluten-related disorders are the umbrella term for all conditions related to gluten ingestion, such as celiac disease and non-celiac gluten sensitivity (NCGS). The prevalence of these diseases has increased over the past 50 years, being an emerging health problem worldwide. Currently, celiac disease is considered the most common food intolerance, prevalence being approximately 1–2% of the population [1]. In contrast, the prevalence of NCGS has been estimated to be as high as 6% of the general population, depending on the population studied [2]. The biological basis of gluten induced symptoms in the absence of celiac disease is unknown but it has been suggested to be related to immune responses to components of wheat apart from gluten, such as wheat amylase-trypsin inhibitors (ATIs) and fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) [2,3].

The main genetic component of celiac disease, HLA-DQ2/DQ8 heterodimers, is well-known. Although these HLA-DQ genes underlie the disorder, only a small percentage of carriers develop the disease and thus, other genetic and environmental factors must be involved in the onset of celiac disease. This review aims to summarize the current knowledge of the contribution of microbiota to pathogenesis and/or onset of CD. In addition, a brief overview of the possible role of the microbiota components on the development and/or onset of NCGS will be provided.

## 2. Celiac disease

Celiac disease is an immune-based enteropathy triggered by ingestion of wheat, rye and barley derived gluten in genetically susceptible individuals. Upon exposure to gluten, inflammatory cascade is induced in the small intestinal mucosa leading to villous atrophy, crypt hyperplasia and increased numbers of lymphocytes in the lamina propria. Disruption of intestinal villus structure leads to impaired epithelial barrier function resulting in nutrient malabsorption that may cause severe symptoms such as anaemia, osteoporosis and, in case of children, to growth retardation. The clinical picture of the celiac disease is highly variable and individual-specific. Classical symptoms of celiac disease include different gastrointestinal symptoms such as abdominal pain and diarrhoea. However, many CD patients are predominantly symptomatic, showing both gastrointestinal and extra-intestinal manifestations. In asymptomatic patients the diagnosis is often delayed and thus the small-bowel mucosal damage may be severe before the celiac disease is suspected. Therefore, early diagnosis of the disease is crucial for the prevention of persistent villous atrophy predisposing to severe complications. Celiac disease is a life-long disease that cannot be cured but the symptoms can disappear and small bowel mucosal damage, intestinal inflammation and epithelial integrity are improved by commitment to a life-long gluten-free diet.

The main genetic predisposition to celiac disease are the human leucocyte antigen (HLA) DQ2 and DQ8 haplotypes. These HLA-DQ genes account for approximately 40% of the genetic risk of celiac disease [4]. However, although these genes underlie the disorder, only a small percentage of carriers develop disease. In addition, the disease concordance in monozygotic twins has been reported to be only 85% [5]. Thus, other genetic and environmental factors must be involved in the onset of the disorder (Fig. 1). Recent genome wide association studies have reported additional 39 non-HLA regions associated with susceptibility to celiac disease development [4]. Interestingly, most of these regions contain genes with immune related functions, several of which are also involved in shaping the intestinal microbiota. In addition, altered expression of non-specific celiac disease risk-genes affecting the host-microbe interactions has recently been reported. For instance, a decreased TOLLIP mRNA levels were observed in untreated celiac patients when compared to healthy controls [6]. TOLLIP is an intracellular protein that inhibits toll-like receptor signalling and failure to upregulate its transcription has been suggested to contribute to the chronic inflammation in celiac and inflammatory bowel disease patients [6,7]. These results suggest the potential role of disturbed host-microbe interaction in the pathogenesis of celiac disease.

It is assumed that aberrant microbiota diversity and relative abundances of specific bacterial taxa lead to functional imbalance where the mutualistic relationship between the host and his microbes is disturbed. Deviations in the microbiota community structure has been associated with several local and systemic diseases, possibly contributing to the pathogenesis and/or clinical manifestation of these

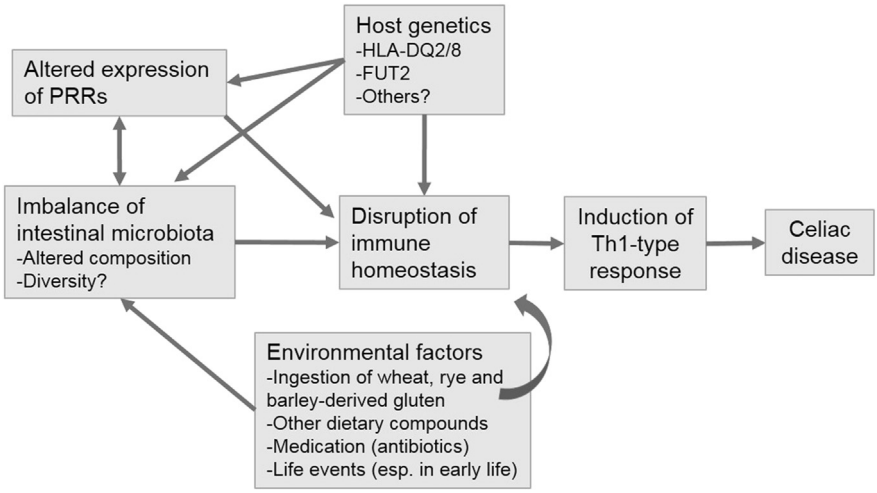


**Fig. 1.** Factors contributing to the onset of celiac disease. Both genetic and environmental factors contribute to the development of celiac disease. Of these, HLA-DQ2 and DQ8 as well as dietary gluten play a direct role in the disturbed immune homeostasis and the subsequent Th1-type immune response required for the disease onset. The other factors either directly or indirectly lead to the intestinal microbiota dysbiosis, which may also promote the development of celiac disease. HLA, human leucocyte antigen; PRRs, pattern recognition receptors.

diseases [8]. A specific role for the intestinal microbiota in celiac disease development has been suggested, but the results remain contradictory [6,9]. This inconsistency may possibly be explained by different techniques used, different sample types analysed (faecal material vs biopsies), patient's age range (infants, children or adults), small sample size and limited amount of studies performed.

### 2.1. *Microbiota in early life and risk of celiac disease*

The initial colonization process of the infant gastrointestinal tract forms the basis for the subsequent microbiota and immune response development, thus having a major influence on the later life health and predisposition to the development of several immune-mediated diseases. Life events occurring in early life and causing disturbances to the developing resident microbiota can lead to long-lasting dysbiosis with increased amounts or relative abundances of one or more disease associated bacterial species. Interestingly, a high frequency of infectious episodes as well as antibiotic treatments, known to affect the intestinal microbiota, have been associated with the onset of celiac disease in genetically susceptible infants [10,11].

It has been suggested that despite the different life events, also a specific disease-biased host genotype may select for the first gut colonizers and thus contribute to the disease risk (Fig. 1). Several studies have reported the influence of genotype of infants at family risk for developing celiac disease (HLA-DQ2 vs non-HLA-DQ2/8 genotype) on the early life faecal microbiota composition [12–14]. In a recent study, 1 month old infants with a high genetic risk for celiac disease were observed to have lower proportion of Actinobacteria and higher proportion of Firmicutes and Proteobacteria than infants with low genetic risk for disease development [14]. Moreover, HLA-DQ genotype seems to specifically influence the colonization process of *Bacteroides* species [12]. In particular, an increased *Bacteroides vulgatus* prevalence was associated with the genotype of infants at high risk of celiac disease development, whereas increased *Bacteroides uniformis* prevalence was associated with a low genetic risk [12]. Indeed, the most constant finding is the higher abundance of *Bacteroides* spp. in celiac disease patients [9,15], although a recent prospective study reported a complete lack of the members of phylum Bacteroidetes in celiac disease predisposed infants [16]. In addition, *Bacteroides fragilis* has been associated with an increased risk for celiac disease development in genetically predisposed

infants who were formula-fed [13]. Interestingly, polysaccharide A produced by *B. fragilis* has been shown to direct the immune system via its ability to direct the development of CD4+ T cells, thus inducing the differentiation of Th1-lineage [17]. Therefore, it seems likely that increased abundance of *Bacteroides* spp. contributes to the Th1 response found in the small intestinal mucosa of celiac disease patients [6,18]. Furthermore, a study by Sanz et al. [19] reported a reduction in immunoglobulin A (IgA) -coated *Bacteroides* spp. in faeces of untreated and treated celiac patients when compared to healthy controls, suggesting that host defences against this bacterial groups may be reduced in celiac disease, thus allowing its increased colonization. Immunoglobulin A is the predominant antibody produced by at mucosal surfaces. Secretory IgA (sIgA) has diverse biological properties such as immune exclusion, immunomodulation and maintenance of the integrity of mucosal barriers. In addition, it provides the first line of defence against invading pathogens by targeting microbial antigens in the mucosal environment. However, the main role of sIgA seems to be the establishment and maintenance of homeostasis with the commensal microbiota [20]. It has been suggested that coating of commensal bacteria by sIgA may represent a mechanism by which this discrimination between abundant normal microbiota and rare pathogens are made [20]. Disrupted production of secretory IgA has been considered a risk factor for the development of gastrointestinal disorders such as celiac disease [21]. IgA is also the most abundant antibody secreted into the breast-milk and the specificities of these sIgAs are shaped by maternal microbiota (reviewed in [22]). Breast milk sIgA provides the first source of antibody-mediated immune protection in the intestine of breast-fed neonate [23]. Transfer of these maternal sIgA to the infant promotes the establishment of regulatory immune system and supports the mutualistic relationship with the commensal microbiota [23]. In addition, the presence of commensal microbes is needed for the induction of the endogenous production of IgA, which is slowly started while the immune system develops [24]. Thus, reduction in intestinal sIgA seems to contribute to microbiota dysbiosis and pro-inflammatory response [24].

Moreover, the reduction of total Gram-positive bacteria population, especially the abundance of *Bifidobacterium* spp. [9,15] and the increase in the proportions of Gram-negative bacteria such as *Clostridium* groups, *Prevotella* spp, and *Escherichia coli* [15,18] have been reported in paediatric celiac disease patients with an active disease. The reduced abundance of bifidobacteria may be of interest, since they have been suggested to alleviate gastrointestinal symptoms of adult celiac patients [25] as well as to reduce abdominal pain in healthy individuals [26]. Microbiota dysbiosis of paediatric celiac disease patients have been suggested to be characterized by an increased microbiota diversity [27], although contradictory finding has recently been reported in a study utilizing high-throughput microarray method [18]. Further studies utilizing the high-throughput methods are needed to comprehensively evaluate the microbiota diversity and species richness associated with celiac disease.

### 2.2. Microbiota in adult celiac disease patients

Although the majority of studies evaluating the microbiota composition associated with celiac disease have been performed with paediatric patients, few studies have also assessed the microbiota in adult CD patients.

Positive seroreactivity against different microbial antigens in celiac disease patients having established small-bowel mucosal damage with villous atrophy and crypt hyperplasia have been reported [28,29]. These serological responses can be detected already in the early stages of the diseases [28], suggesting that immune responses to commensal microbiota are already present early in the disease stage and thus may have a role in the pathogenesis of the celiac disease and the development of mucosal damage.

The role of intestinal microbiota on different clinical manifestations of the disease was demonstrated in a study by Wacklin et al. [30], where the microbiota composition, structure and diversity were observed to differ depending on the manifestation of the disease, especially between intestinal symptoms (gastrointestinal symptoms or anaemia) and extra-intestinal symptoms (dermatitis herpetiformis). The patients with classical gastrointestinal symptoms had a higher amount of Proteobacteria than patients with other manifestation of the disease, whereas patients with anaemia had the lowest microbial richness and distinct clustering of duodenal microbiota profiles.

After a gluten-free diet is initiated, healing of the intestinal mucosa usually starts. Mucosal healing is a gradual process and it has been estimated that the median time needed to achieve a normal villous height is 3.8 years [31]. However, a significant fraction of celiac disease patients suffer from persistent symptoms despite an adherence to a gluten-free diet and normalized small bowel mucosa [32]. In some patients, symptoms can be explained by inadvertent gluten intake or the presence of additional gastrointestinal disease [33]. In many cases the reason for persistent symptoms cannot be explained [32]. Microbiota dysbiosis observed in untreated celiac patients is not completely restored after adherence to a gluten-free diet, suggesting that some changes in microbiota are not secondary to the inflammatory milieu of the active phase of the disease but could play a primary role in predisposition to celiac disease development [15,34]. Treated celiac disease patients with persistent symptoms have been reported to have a microbiota dysbiosis, characterized by Proteobacteria-dominating duodenal microbiota and reduced microbial richness compared to treated patients without symptoms [35].

It has been suggested that the IL17A producing cells play a major role in the pathogenesis of celiac disease, that both gluten and CD associated bacteria provoke an IL-17A response in the intestinal mucosa of CD patients and that the magnitude of the adverse IL-17A reaction to gluten is markedly influenced by the composition of the resident microbiota and the amount of CD associated bacteria present [36]. In their study, Sjöberg et al. [36] used a mixture of CD associated bacteria (five *Prevotella*, one *Lachnoanaerobaculum* and one *Actinomyces* isolate) and gluten to challenge the biopsies taken from untreated and treated CD patients and from clinical controls. At diagnosis, patients with CD were observed to have highly elevated levels of IL-17A mRNA in their jejunal mucosa. The levels returned to normal level on a gluten-free diet [36]. The celiac disease associated bacteria analysed in that study were capable of inducing an IL-17A response on their own, suggesting that this response seen in active celiac disease could be (in part) directed against the CD -associated bacteria. In addition, these bacteria determined the magnitude of the IL-17A response (either suppressing or enhancing) depending on whether the patient had a strong response to gluten digest alone or not. Interestingly, all patients that showed a suppressed IL-17A response were observed to be born during the Swedish celiac disease epidemic, whereas children born after the epidemic showed contradictive response.

Homozygosity for non-functional fucosyltransferase 2 (FUT2) gene leads to the absence of ABH blood groups (FUT2 non-secretor status) in body fluids. Recently, FUT2 non-secretor status has been associated with the susceptibility to celiac disease in the Finnish population [37]. Moreover, FUT2 secretor status has been shown to be a major determinant for the gut microbiota richness and the composition of abundant microbiota in healthy individuals [38,39] as well as in Crohn's disease patients [40]. Interestingly, recovery after the pathogenic infection was slower in FUT2 deficient mice when compared to FUT2 sufficient controls [41]. These results suggest that fucosylation of intestinal epithelial cells may be a protective mechanism that maintains the host-microbial interactions, thus preventing the development of microbiota dysbiosis. For comprehensive conclusions considering the role of intestinal microbiota in adult celiac disease patients, further studies utilizing high-throughput analysis are needed.

### 2.3. Effect of gluten-free diet on microbiota

Currently, the only effective treatment available for celiac disease is a life-long adherence to a gluten-free diet. Although the diet is effective and safe, it also creates social and economic burdens to the patients and some reports have shown that intestinal microbiota is also affected [15,42,43]. Microbiota deviations observed in untreated celiac disease patients were only partly restored after long-term treatment with gluten-free diet. In young children (6–12 years of age), who had followed gluten-free diet for two years, a higher diversity and a complete rearrangement in *Eubacterium* species community as well as changed metabolomics profiles were observed [43]. In contrast, the abundances of *E. coli* and *Staphylococcus* were observed to normalize after dietary treatment [15]. Another study reported slightly different microbiota shifts, including decreased abundance of bifidobacteria, lactobacilli, *Clostridium lituseburense* and *Faecalibacterium prausnitzii*, whereas proportions of *E. coli* and Enterobacteriaceae increased [42]. Majority of these microbiota changes are most likely caused by a dietary effect, since transition to a gluten-free diet is associated with a reduced intake of complex polysaccharides. Although a long-term change in dietary habits is required to provoke major shifts in

intestinal microbiota composition, changes in daily carbohydrate intake may affect specific groups of bacteria over a short period of time. For example, consumption of inulin or resistant starch increases the levels of *Bifidobacterium* spp. and *Faecalibacterium prausnitzii* or *Ruminococcus bromii* and *Eubacterium rectale*, respectively [8]. These non-digestible carbohydrates are fermented in the colon by its microbiota to yield energy for microbial growth and end products such as short-chain fatty acids (SCFAs), mainly acetate, propionate and butyrate. SCFAs have a profound impact on gut health as an energy source, an inflammation modulator, a vasodilator and part of gut motility and wound healing. In addition, they are energy substrates for the colonic epithelium (butyrate) and peripheral tissues (acetate and propionate). The patterns of intestinal fermentation and consequently the types and amounts of SCFAs produced are determined by how much carbohydrate is consumed and the composition of intestinal microbiota [44]. Further studies are needed to shed light into the role of these host-microbiome interactions in the pathogenesis of celiac disease and other immune-mediated diseases.

## 3. Non-celiac gluten sensitivity

The prevalence of NCGS patients is an emerging health problem and it has been estimated to account over 6% of the general population, depending on the population studied [2]. However, the real prevalence of NCGS remains obscure. Currently the risk factors for NCGS have not been established, although the disorder has a tendency to be associated with female gender and young or middle age [45]. Non-celiac gluten −sensitive individuals develop adverse reactions such as gastrointestinal and extra-intestinal symptoms after exposure to gluten [46]. Typical gastrointestinal symptoms include abdominal pain, bloating and altered bowel habit, the most often reported extra-intestinal symptoms being fatigue, headache, joint or bone pain, mood disorders and skin manifestations [2,45]. Due to the similarities in clinical outcomes and the absence of diagnostic biomarkers, it is challenging to differentiate NCGS from other gluten related disorders. Typically the diagnosis of NCGS is made after the exclusion of celiac disease and wheat allergy by means of negative celiac serology, negative histological findings and negative testing for specific immunoglobulin E (IgE). The diagnosis is further confirmed by a positive oral gluten challenge after exclusion of gluten from the diet for few weeks. The gluten challenge should be implemented in a blinded fashion in order to avoid a possible placebo effect commonly seen in the dietary interventions [2]. However, this approach lacks specificity and is difficult to carry out in clinical practise. In addition, the exclusion of irritable bowel syndrome (IBS) should be considered during the diagnostic process, since gluten may exacerbate the symptoms in these patients [47]. In contrast, grain-free diet or diet low in FODMAPs have been shown to alleviate the symptoms in some IBS patients [48].

Although the aetiology of NCGS is unknown, it has been hypothesized that NCGS involves innate immune mechanisms without any implication of adaptive immune response [49]. This is in contrast to celiac disease where overexpression of adaptive immunity markers is detected. Previously it has been shown that NCGS patients have normal intestinal permeability, normal expression of tight junction proteins claudin-1 and ZO-1 and significantly higher expression of claudin-4 when compared to celiac disease patients [46]. The upregulation of claudin-4 coincided with the increased expression of toll-like receptor (TLR) proteins TLR1, TLR2 and TLR4 and decreased amount of regulatory T cells when compared to celiac disease patients [46]. Toll-like receptors are molecular pattern recognition receptors often residing in the epithelial cell surface that recognize microbe-associated molecular patterns (MAMPs). The dynamic host-microbe interaction mediated by these receptors is crucial for the maintenance of intestinal homeostasis. Moreover, intestinal microbes have been shown to decrease the intestinal permeability by upregulating the expression of tight junction proteins [50]. Since intestinal microbiota has an essential role in regulating the antigen milieu of enterocytes, it may contribute to the pathogenesis or onset of non-celiac gluten sensitivity. However, its role in the NCGS has not yet been studied.

## 4. Conclusion

Several studies have demonstrated an altered intestinal microbiota composition in celiac disease patients. However, there is still no consensus yet regarding the special microbial species affecting

positively or negatively to the disease process. In addition, human studies tend to be correlative and thus evidence supporting the causality between specific bacteria and the pathogenesis of certain diseases are difficult to obtain. Majority of the studies reporting association of microbiota with celiac disease have been carried out with paediatric patients, whose microbiota is still developing and prone to the compositional fluctuation due to the influence of a variety of environmental factors. Thus, studies considering the mature, established microbiota of adult patients are warranted. Moreover, studies including larger sample sizes and utilizing the newest state-of-the-art methods are needed to comprehensively analyse the role of the intestinal microbiota and its metabolites in both celiac disease and NCGS.

## Conflict of interest

None.

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